REMARKS

Claims 49-53 are pending in the present application. Claim 49 has been amended to correct a clerical error. Support for the amendment can be found in the specification of the instant application, *e.g.*, at page 25, lines 11 to 17. Claims 51 and 52 have been amended to delete the recitation of "key" in the wording "key regulatory domain." Claim 50 has been deleted and claims 54 to 56 have been added instead. New claims 57 to 70 have been added. Support for the new claims can be found in the specification as set forth in the chart below. Thus, no new matter has been introduced. Upon entry of the present Amendment, claims 49 to 70 will be pending in the present application.

Claim	Support
57	Page 34, lines 13-22; page 75, line 10; page 30, line 28 to 29
58	Page 34, lines 13-16
59-68	Page 34, lines 18-22; page 75, line 10; page 30, line 28 to 29
69	Page 30, lines 7-8; page 75, line 10; page 30, line 28 to 29
70	Page 5, line 31

THE OBJECTIONS TO THE SPECIFICATION SHOULD BE WITHDRAWN

Applicants' claim for priority has been objected to because the relationship between the priority applications, Application Serial No. 09/161,122, filed September 25, 1998 and Application Serial No. 08/316,439, filed September 30, 1994, now U.S. Patent No. 5,840,520, issued November 24, 1998, is not indicated. Applicants have amended the specification to clarify that Application Serial No. 09/161,122, filed September 25, 1998 is a continuation-in-part of Application No. 08/316,439, filed September 30, 1994, now U.S. Patent No. 5,840,520, issued November 24, 1998. Thus, Applicants respectfully request that the objection relating to Applicants' claim to priority be withdrawn.

The specification has further been objected to because it allegedly lacks antecedent basis for the claim language "an mRNA coding sequence operatively linked to a polymerase binding site of a respiratory syncytial virus." The specification has been amended herein to incorporate the antecedent basis for the claim language from originally filed claim 17.

THE REJECTION UNDER 35 U.S.C. § 112, SECOND PARAGRAPH, SHOULD BE WITH DRAWN

Claims 51 and 52 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention allegedly because multiple interpretations of the claim language "key regulatory domain" and "key functional domain" are possible. In particular, the Examiner contends that (i) it is not clear whether the term "key" refers to the domain's importance to a particular gene or to the virus as a whole; and (ii) it is unclear what genes are included by this description.

With regard to the first issue that the term "key" is ambiguous, Applicants respectfully point out that the term "key" has been deleted from the claims and the issue is therefore moot.

Further, with regard to the second issue, Applicants respectfully direct the Examiner's attention to page 34, lines 18 to 22, of the specification as originally filed:

> The genetic alterations required to cause virus attenuation may be gross (e.g., translocation of whole genes and/or regulatory sequences within the virus genome), or minor (e.g., single or multiple nucleotide substitution(s), addition(s) and/or deletion(s) in key regulatory or functional domains within the virus genome), as further described in detail.

Dependent claims 51 and 52 further define genetic alteration as a genetic alteration in a functional or regulatory domain. Thus, the genetic alterations in regulatory or functional domains are of such nature that they cause virus attenuation. The Examiner's concerns are overcome because the genes that are included are genes whose mutation could result in attenuation of the virus. As attenuation of the virus can be achieved by, *e.g.*, reducing the efficiency of replication of the viral genome, expression of viral proteins and/or infectivity of the virus, all genes involved in these processes are included.

With regard to the M2-1 gene, the Examiner contends that it is unclear whether M2-1 is included as a key domain. Applicants respectfully direct the Examiner's attention to page 6, lines 12 to 13 of the application as filed. Because attenuation of the virus can be achieved by mutagenesis of the M2-1 gene, genetic alterations of key regulatory or key functional domains can also be genetic alterations of the M2-1 gene.

Thus, Applicants respectfully request that the rejection of claims 51 and 52 under 35 U.S.C. § 112, second paragraph, be withdrawn.

THE REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH, SHOULD BE WITH DRAWN

Claims 49-53 are rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly fails to provide enablement for anti-RSV vaccine compositions. The gravamen of the rejection is that the art does not presently accept a particular animal model as predictive of human responses to RSV vaccines. Applicants respectfully disagree because RSV infection in chimpanzees is an accepted animal model for RSV infections in humans and efficacy of vaccines of the invention has been shown in chimpanzees.

RSV infection in chimpanzees is an accepted model for RSV infection in humans; Dudas *et al.*, 1998, Clinical Microbiology Reviews 11:430-439 ("Dudas") states, *e.g.*, at page 434, left column, 2nd full paragraph: "[a]s a model for immunization of young infants who have maternally derived RSV antibody, chimpanzees were infused with RSVIG, . . . " Thus, RSV infection in chimpanzees is accepted by the skilled artisan as a model for RSV infection in humans.

That the compositions of the invention can be successfully used to protect chimpanzees from RSV infection has been shown in Teng et al., 2000, Journal of Virology 74(19): 9317-9321 ("Teng," attached as Exhibit A). In their study, Teng tested the protective efficacy of recombinant RSV with an inactivated NS1 or M2-2 gene (designated rA2ΔM2-2 and rA2ΔNS1, respectively) in the upper and lower respiratory tracts of chimpanzees. Attenuation and immunogenicity of rA2ΔM2-2 and rA2ΔNS1 are shown in Table 1 at page 9319 of Teng and protection against challenge with wild type RSV is demonstrated by the data shown in Table 2 at page 9319 of Teng.

Applicants respectfully invite the Examiner's attention to section 2164.02 of the MPEP:

> "[...] if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate."

As RSV infection in chimpanzees is an art accepted model for RSV infection in humans and efficacy of vaccines of the invention has been shown in chimpanzees (see, *e.g.*, Teng), the presently claimed invention meets the requirements under 35 U.S.C. § 112, first paragraph.

The Examiner cites Prince et al., 2000, Journal of Virology, 74(22): 10287-10292 ("Prince") to support the contention that there are not effective anti-RSV vaccines for humans. Prince briefly summarizes the problems associated with replicating RSV vaccines (first paragraph at page 10287). These problems, however, have been overcome by the present invention as demonstrated by the successful application of the vaccines of the present invention in chimpanzees (see Teng). Further, Prince describes the efficacy and safety of a subunit vaccine, the extramembrane domains of the F and G glycoproteins (FG). Thus, Prince is concerned with non-replicating RSV vaccines and can therefore not be compared with the replicating RSV vaccines of the present invention.

The Examiner further cites Tang et al., 2003, Journal of Virology 77(20): 10819-10828 ("Tang") to support the contention that there are not effective anti-RSV vaccines for humans. Applicants were unable to locate any such statement in Tang. Applicants believe that the Examiner might conclude from the fact that work is still being conducted to identify new anti-RSV vaccines that no effective RSV vaccines for humans are in existence. Such a conclusion, however, is inapposite as continuing research on a subject cannot possibly mean that previous reports of successful applications (*e.g.*, Teng discussed above) are to be ignored.

Applicants have demonstrated that the compositions of the invention are immunogenic (see, *e.g.*, pages 118 and 120 of the specification), *i.e.*, stimulate the production of antibodies against RSV, therefore, the compositions of the invention have also protective properties against re-infection by RSV. Dudas states that "the rate of reinfection with RSV and the rate of [lower respiratory tract illness] at the time of reinfection also correlate inversely with the level of serum neutralizing antibody against RSV" (at page 431, the sentence spanning the left and right columns). As the presence of anti-RSV neutralizing antibodies prevents the recurrence of reinfection with RSV and the rate of lower respiratory tract illness, the compositions of the invention have vaccinating properties.

Applicants further submit that the description found in the specification as filed is adequate since the specification is enabled for vaccine compositions for inducing protective immunity in mammals other than humans. Under Section 112, it is not fatal that a certain amount of experimentation may be required to adapt the invention to a specific purpose, provided the experimentation is routine. In re Wands, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). Moreover, considerable amount of experimentation is permitted if it is merely routine or the specification provides a reasonable amount of guidance and direction to

perform such experimentation. In re Jackson, 217 U.S.P.Q. 804, 807 (PTO Bd. Pt. App. Int. 1982).

Applicants submit that the specification contains an adequate description of the invention to enable the claims as currently pending. The provisions of Section 112, first paragraph, require that the description "enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same . . . (emphasis added). Applicants submit that any person skilled in the art of molecular biology can readily construct the recombinant viruses for use in vaccines as claimed by use of knowledge common in the art and in view of the teaching of the present specification. The specification also provides ample disclosure to allow one of skill in the art to assay the claimed vaccines to ensure that they are producing a protective immune response. See for example the specification of the instant application at page 108, line 25 to page 110, line 2.

Further, Applicants respectfully point out that procedures for testing a vaccine are routine in the art, and that the skilled artisan would be able to determine without undue experimentation which of the vaccines covered by the pending claims confer immunity to a subject when administered as a vaccine. In the context of this argument, the Applicants would like to direct the Examiner's attention to *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing *In re Angstadt*, 537 F.2d 489, 502-04, 190 USPQ 214, 217-19 (CCPA 1976)):

> " 'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.' "

Thus screening procedures to test the vaccines of the invention for their potential to protect against viral infections and to confer immunity to a particular pathogen to a subject should not be considered undue experimentation since such procedures are well-known to the skilled artisan.

The Examiner further states the *Brooktree v. Advanced Micro Devices*, 24 U.S.P.Q.2D 1401 (Fed. Cir. 1992) decision does not apply to the present rejection because *Brooktree* relates to a rejection under 35 U.S.C. 101 whereas the present rejection was made under 35 U.S.C. 112. Applicants respectfully assert that *Brooktree* applies because even though the rejection was made under 35 U.S.C. 112, the rejection is based on the Examiner's conclusion that at least part of the claimed compositions are inoperable. The Examiner

appears to contend that the operability of the presently claimed compositions has not been shown because the animal model used by Applicants in the application is allegedly not predictive of the success of the methods for the treatment of RSV infections in humans. Therefore, the Examiner's rejection under 35 U.S.C. § 112, 1st paragraph, is a rejection based on alleged lack of utility of the claimed methods.

Further, the Examiner's attention is directed to the opinion of the Court of Appeals for the Federal Circuit (Federal Circuit) in *In re Brana*, 34 U.S.P.Q.2d 1437 (Fed. Cir. 1995). In *Brana*, the Board had affirmed a final rejection under Section 112, 1st paragraph, of claims covering certain compounds asserted to be useful as anti-tumor substances because it was alleged that the specification was non-enabling since it did not sufficiently establish that the claimed compounds had a practical utility, *i.e.*, as anti-tumor agents. 34 U.S.P.Q.2d at 1439.

The Federal Circuit emphatically reversed the Board's decision. First, it explained the legal standard for compliance with the relevant Section 112 requirement, explaining that "unless there is reason to doubt the objective truth of the statements contained [in the specification] which must be relied on for enabling support", a specification's disclosure "must be taken as in compliance with the enabling requirement." *Id.* at 1441 (emphasis in the original). Further, the *Brana* Court made clear that the Patent and Trademark Office has the initial burden of challenging a presumptively correct assertion of utility; evidence must be presented that those of skill in the art would doubt the disclosure. Only then must the applicant provide rebuttal evidence.

Second, the Federal Circuit explained that even if one of skill in the art would have questioned the asserted utility, all applicants need do to overcome the rejection is to proffer sufficient evidence to convince one skilled in the art of the asserted utility. *Id.* at 1441.

In the *Brana* situation, the Court found that the Patent and Trademark Office had not met its initial burden. Further, the Court held that even if the Patent and Trademark Office had met its burden, the evidence proffered was clearly sufficient to meet the statutory requirement. As explained by the Court:

> We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans. *Id.* at 1442 [quoting *In re Krimmel*, 292 F.2d 948, 953 (CCPA 1961)].

The Federal Circuit further reminded the Commissioner that testing for the full safety and effectiveness of a product is more properly left to the Food and Drug Administration and the requirements under the law for obtaining a patent should not be confused with the requirements for obtaining government approval to market a particular drug for consumption. 34 U.S.P.Q.2d at 1442; *see also Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994). In light of the *in vivo* rodent and primate protection data in the specification, the Examiner is clearly requiring human clinical testing in order to fulfill the enablement requirement. This standard is inappropriate under the law. *Brana, supra; Scott v. Finney, supra.* Moreover, it is unwarranted by the references cited by the Examiner, in contrast to the assertions in the Office Action.

As discussed above, RSV infection in chimpanzees is an art accepted model for RSV infection in humans and efficacy of vaccines of the invention has been shown in chimpanzees (see, *e.g.*, Teng).

Applicants therefore respectfully request that the rejection under 35 U.S.C. 112, first paragraph, be withdrawn.

THE REJECTION UNDER 35 U.S.C. § 102(a) SHOULD BE WITH DRAWN

Claims 49, 50, and 52 are rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Crowe et al., 1994, Vaccine 12:691-699 ("Crowe 1") in light of Murphy (U.S. Patent 5,993,824). Applicants submit herewith a copy of a declaration by Dr. David K. Clarke under 37 C.F.R. § 1.131 (the "Clarke Declaration") to establish a date of invention prior to the publication date of Crowe 1 , *i.e.*, June 1994. The Clarke Declaration was originally filed in copending patent application 09/724,388 (the "'388 Application"). The '388 Application is a divisional of U.S. Patent Application No. 09/161,122 (the "'122 Application"). The '122 Application is also a priority application of the present application. Further, Dr. Clarke is named as an inventor in the present application.

Copies of Exhibits A1, A2, B to E were submitted along with the Carke Declaration in the '388 Application. Because the Examiner is in already possession of the Exhibits, Applicants do not submit another set of copies of the Exhibits of the Clarke Declaration. However, should the Examiner require copies of the Exhibits, the Examiner is respectfully invited to contact the undersigned and request such copies. Even though paragraph 9 of the Clarke Declaration states that Exhibit F sets forth a summary of the work described in

Exhibits C to E, the contents of Exhibit F can be found in paragraphs 7a to 7r and Exhibit F was has not been submitted.

The Clarke Declaration provides evidence to show that Applicants had a date of invention prior to the publication date of Crowe 1. Thus, the Crowe 1 reference is not available as prior art under 35 U.S.C. § 102(a) against claims 49, 50, and 52.

Claims 49 to 52 are rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Crowe et al., 1994, Vaccine 12(9): 783-790 ("Crowe 2") in light of Murphy (U.S. Patent 5,993,824). The Clarke Declaration establishes a date of invention prior to the publication date of Crowe 2, *i.e.*, July 1994. In particular, the Clarke Declaration provides evidence to show that Applicants had a date of invention prior to the publication date of Crowe 2. Thus, the Crowe 2 reference is not available as prior art under 35 U.S.C. § 102(a) against claims 49 and 52.

Applicants respectfully request that the rejections under 35 U.S.C. § 102(a) of claims 49 to 53 should be withdrawn.

CONCLUSION

Applicants respectfully request entry and consideration of the foregoing amendments and remarks. No new matter has been introduced. The claims are believed to be free of the art and patentable. Withdrawal of all the rejections and an allowance are earnestly sought.

Respectfully submitted,
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Date: July 20, 2004

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